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(54) Title: PHARMACEUTICAL AND/OR COSMETIC COMPOSITIONS FOR THE TREATMENT OF LOCALISED ADIPOSITIES AND CELLULITE

(57) Abstract: The present invention relates to pharmaceutical and/or cosmetic compositions containing a combination of the following active principles: a) complex of escin/beta-sitosterol with phospholipids, b) complex of *Ginkgo biloba* dimeric flavonoids with phospholipids, c) complex of *Centella asiatica* triterpenes with phospholipids, and optionally one or both of: d) ethyl ximeninate, e) *Coleus forskolii* standardized extract.

**PHARMACEUTICAL AND/OR COSMETIC COMPOSITIONS FOR
THE TREATMENT OF LOCALISED ADIPOSITIES AND
CELLULITE**

The present invention relates to pharmaceutical and/or cosmetic compositions for the treatment of localised adiposities and cellulite.

Localised adiposities and cellulite affect a remarkable, increasing percentage of the western population, mainly women. Cellulite, in 5 particular, also affects many normal weight-constitution, adult women without obesity problems. These problems are connected to panniculopathy conditions characterized by poor peripheral circulation, edema, fibrosis and altered lipocytes metabolism, therefore an ideal treatment should take into account all these factors.

10 The huge number of pharmaceutical or cosmetic formulations for the treatment of localised adiposities and cellulite currently available on the market have not so far solved satisfactorily the problem of localised adiposities and cellulite. Said compositions are generally based on active principles of vegetable origin, such as ivy, horse-chestnut, cola extracts; 15 caffein, beta-adrenergic stimulants, methylxanthines, and the like. Nevertheless, none of said compositions has proved so far really effective, and the results obtained are often due to the dietetic regimen generally associated to said treatments, rather than to the use of said compositions.

It has now been found, and this is the object of the present invention, that 20 pharmaceutical and/or cosmetic topical compositions containing a combination of active principles of vegetable origin provide excellent results in the treatment of localised adiposities and cellulite, drastically reducing cutaneous fat deposits and "orange-peel" skin, due to the combination of the different activities of the various components, which exert anti-edematous, antiphosphodiesterase,

vasokinetic activities and promote collagen production.

The components of the compositions of the present invention are all known and used in pharmacy and/or in cosmetics, nevertheless it is to be noted that the activity of said single components, when used separately, is by far 5 lower than that achieved with the compositions of the present invention; on the contrary, a synergistic effect among said various components is observed.

In particular, the present invention provides pharmaceutical and/or cosmetic topical compositions containing as active principles escin / beta-sitosterol complexes with phospholipids, *Ginkgo biloba* dimeric flavonoids 10 complexes with phospholipids, ethyl ximeninate, *Coleus forskolii* extracts and *Centella asiatica* triterpenes complexes with phospholipids.

More particularly, the present invention relates to pharmaceutical and/or cosmetic compositions containing a combination of the following active principles:

- 15 a) complex of escin/beta-sitosterol with phospholipids,
- b) complex of *Ginkgo biloba* dimeric flavonoids with phospholipids,
- c) complex of *Centella asiatica* triterpenes with phospholipids,
and optionally one or both of:
- d) ethyl ximeninate,
- 20 e) standardized *Coleus forskolii* extract.

According to a preferred embodiment of the present invention, the compositions of the present invention have the following percentage composition:

- a) complex of escin/beta-sitosterol with phospholipids: 0.1 - 2.5%;
- 25 b) complex of *Ginkgo biloba* dimeric flavonoids with phospholipids:
0.1 - 2.5%;
- c) complex of *Centella asiatica* triterpenes with phospholipids: 0.1 - 2.5%,
and optionally one or both of:

- d) ethyl ximeninate: 0.1 - 2.5%;
- e) *Coleus forskolii* standardized extract: 0.1 - 2.5%.

Escin is a saponin contained in horse-chestnut seeds, endowed with remarkable anti-edematous properties, probably due to a modification of the capillary permeability: it has in fact been shown that escin is capable of reducing the number and the diameter of the pores of the capillary walls through which water exchange occurs. Therefore, escin properties are considered useful in the treatment of the localised edematous conditions typical of cellulite and of localised adiposities.

10 The complex of escin/beta-sitosterol with phospholipids, disclosed in EP 0 283 713, has the same action as escin, but shows a more prolonged release of the active principles and improved bioavailability.

15 The complex of *Ginkgo biloba* dimeric flavonoids with phospholipids, disclosed in EP 0 275 005, has the same activity as the dimeric *Ginkgo biloba* flavones in the free form, but shows a more prolonged release of the active principles and better bioavailability. *Ginkgo biloba* dimeric flavonoids are extremely potent vasoactive agents due to their inhibitory action on the release of histamine and of the enzyme cAMP phosphodiesterase from mast cells. The inhibition of this enzyme involves 20 an increase in the level of cAMP, a molecule able to activate lipocytes metabolism. This complex therefore exerts a lipolytic action and improves the microvascular perfusion and the cutaneous trophism.

25 *Centella asiatica* triterpenes (asiatic acid, asiaticoside and madecassic acid) exert a beneficial action on the production of collagen (in the stable form) by dermal fibroblasts, by increasing the absorption of hydroxyproline, which is fundamental for collagen synthesis, thereby contrasting the cutaneous sclerosis responsible for the formation of the "orange-peel skin" typical of cellulite. The complex of *Centella asiatica* triterpenes with

phospholipids disclosed in EP 0 283 713 provides prolonged release and better penetration in the dermis.

Ethyl ximeninate is the ethyl ester of ximeninic acid, a fatty acid which can be found in *Olax dissitiflora* and in other oleaginous plants of the genus *Ximenia*.

5 Advanced capillaroscopic techniques have shown that ethyl ximeninate has a significant vasokinetic activity. This, combined with the activity of the other active principles of the formulation, is useful in the treatment of cellulite.

The standardized *Coleus forskolii* extract, described in example 1, contains forskolin, a well-characterized molecule able to stimulate adenylate 10 cyclase activity and therefore to increase the concentration of cyclic nucleotides, molecules which stimulate lipolysis and haematic flow at microvascular level.

The compositions of the invention will be applied topically on body areas affected by localised adiposities and/or cellulite, for time periods 15 ranging from some days to some months, depending on the severity of the disorder to be treated, with frequency of 1 - 2 applications a day.

The compositions of the invention will be formulated, according to conventional techniques, in the form of cream, oil, gel, foam, emulsion, milk and the like, optionally encapsulated in liposomes. Said compositions will contain the 20 excipients conventionally used in pharmaceutical and/or cosmetic technology.

Examples of formulations are reported hereinbelow.

Example 1 - Preparation of a 20% forskolin standardized extract of *Coleus forskolii*

1 kg of rhizomes and roots of *Coleus forskolii*, finely ground, are 25 extracted using subsequently 10 l of CO₂ under continuous recycle, for 2 hours at a temperature of 45°C and a pressure of 240 bars. After evaporation of the solvent at 50°C, the residue is dissolved in 5 volumes of hexane and back-extracted twice with 2 volumes of 90% v/v methanol.

The methanolic extract is concentrated to dryness to obtain 45 g of an extract containing 20% of forskolin.

Example 2 - Cream formulation.

100 g of cream contain:

5	Complex of escin/beta-sitosterol with phospholipids	1.50 g
	Complex of <i>Centella asiatica</i> triterpenes with phospholipids	0.50 g
	Complex of dimeric <i>Ginkgo biloba</i> flavonoids with phospholipids	0.50 g
	<i>Coleus forskolii</i> standardized extract (20% forskolin)	0.50 g
	Ethyl ximeninate	0.50 g
10	C12-C15 alkyl benzoate (Finsolv TN - Finetex)	7.50 g
	Cyclomethicon (Belsil CMO40 - Wacker)	6.00 g
	Ethoxydiglycole (Transcutol CG - Gattefossè)	5.00 g
	Glyceryl stearate and PEG-100 stearate (Arlacel 165 V-ICI)	3.00 g
	Karité butter (Shea butter) (Dekarité - Jan Dekker)	3.00 g
15	Polysorbate 60 (Tween 60 - ICI)	2.00 g
	Cetyl alcohol	1.00 g
	Avocado oil (Avocado oil - Jan Dekker)	1.00 g
	Vitamin E acetate	0.20 g
	Ascorbyl palmitate	0.10 g
20	Polyacrylamide (e) C13-14 isoparaffin (e)	
	Laureth-7 (Sepigel 305 - Seppic)	3.00 g
	Imidazolidinylurea	0.30 g
	Methylchloroisothiazolinone (and) methylisothiazolinone	
	(Kathon CG - Rohm & Haas)	0.05 g
25	Bisodic EDTA	0.10 g
	BHT	0.05 g
	Perfume (162 - AGF)	0.20 g
	Depurated water	q.s. to 100 g

CLAIMS

1. Pharmaceutical and/or cosmetic compositions containing:
 - a) complex of escin/beta-sitosterol with phospholipids,
 - 5 b) complex of *Ginkgo biloba* dimeric flavonoids with phospholipids,
 - c) complex of *Centella asiatica* triterpenes with phospholipids,
and optionally one or both of:
 - d) ethyl ximeninate,
 - e) *Coleus forskolii* extract.
- 10 2. Compositions as claimed in claim 1, having the following percentage composition:
 - a) complex of escin/beta-sitosterol with phospholipids: 0.1 - 2.5%;
 - b) complex of *Ginkgo biloba* dimeric flavonoids with phospholipids: 0.1 - 2.5%;
 - c) complex of *Centella asiatica* triterpenes with phospholipids: 0.1 - 2.5%,
15 and optionally one or both of:
 - d) ethyl ximeninate: 0.1 - 2.5%;
 - e) *Coleus forskolii* extract: 0.1 - 2.5%.
3. Composition as claimed in claims 1 and 2, containing:
 - a) complex of escin/beta-sitosterol with phospholipids 1.50 g
 - 20 b) complex of *Centella asiatica* triterpenes with phospholipids 0.50 g
 - c) complex of dimeric *Ginkgo biloba* flavonoids with phospholipids 0.50 g
 - d) *Coleus forskolii* standardized extract (20% forskolin) 0.50 g
 - e) ethyl ximeninate 0.50 g
4. Compositions as claimed in claims 1 and 2 wherein the extract of *Coleus*
25 *forskolii* is a 20% forskolin standardized extract.
5. A method for the cosmetic treatment of localised adiposities and/or cellulite, which comprises the application of a composition as claimed in claims 1 - 4 on the areas to be treated.

INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 19158 A (CETERIS HOLDING B V AMSTERDAM ;MERIZZI GIANFRANCO (IT)) 22 March 2001 (2001-03-22) page 6, line 15 - line 26 page 3, line 26 - line 28 page 9; claims 1,6 -----	1-5
Y	US 5 194 259 A (SOUADANT ETIENNE ET AL) 16 March 1993 (1993-03-16) column 2, line 67 -column 3, line 5; claims 1,2,4; example 8 -----	1-5

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	REILLY W ET AL: "BODY CONTOURING USING AN ORAL HERBAL ANTIOXIDANT FORMULATION - CENTELAPLUS: A DOSE CONTROLLED OBSERVATIONAL STUDY" REDOX REPORT, CHURCHILL LIVINGSTONE, EDINBURGH, GB, vol. 5, no. 2/3, 2000, pages 144-145, XP000990069 ISSN: 1351-0002 the whole document -----	1-5
Y	BOMBARDELLI E ET AL: "PHYTOSOMEs in functional cosmetics." FITOTERAPIA, vol. 65, no. 5, 1994, pages 387-401, XP001105302 ISSN: 0367-326X part "Effects on microcirculation" -----	1-5
Y	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 12, 31 October 1998 (1998-10-31) & JP 10 182473 A (LION CORP), 7 July 1998 (1998-07-07) abstract -----	1-5
Y	BOMBARDELLI E ET AL: "Microvasculokinetic activity of ximenynic acid ethyl ester." FITOTERAPIA, vol. 65, no. 3, 1994, pages 195-201, XP001104828 ISSN: 0367-326X page 196, line 3 - line 9; figure 3 -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/05390

Patent document cited in search report	Publication date		Patent family member(s)		Publication date
WO 0119158	A 22-03-2001		AU 7418800 A		17-04-2001
			BR 0014262 A		09-07-2002
			WO 0119158 A2		22-03-2001
			EP 1214084 A2		19-06-2002
US 5194259	A 16-03-1993		FR 2669537 A1		29-05-1992
			CA 2056322 A1		29-05-1992
			DE 69111781 D1		07-09-1995
			DE 69111781 T2		02-05-1996
			EP 0493151 A1		01-07-1992
			ES 2077827 T3		01-12-1995
			JP 3091782 B2		25-09-2000
			JP 5221842 A		31-08-1993
JP 10182473	A 07-07-1998		NONE		